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Spinal Cord Mechanisms of Chronic Pain and Clinical Implications

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Abstract

Chronic pain is a prevalent and challenging problem for most medical practitioners. Due to complex pathological mechanisms involved in chronic pain, optimal treatment is still under development. The spinal cord is an important gateway for peripheral pain signals transmitted to the brain. In chronic pain states, painful stimuli trigger afferent fibers in the dorsal horn to release neuropeptides and neurotransmitters. These events induce multiple inflammatory and neuropathic processes in the spinal cord dorsal horn and trigger modification and plasticity of local neural circuits. As a result, ongoing noxious signals to the brain are amplified and prolonged, a phenomenon known as central sensitization. In this review, the molecular events associated with central sensitization as well as their clinical implications are discussed.

Introduction

Nociception or pain perception is a protective mechanism for preventing potential damage to an organism. Nociception is essential for an organism to detect harmful stimuli and to respond adequately for survival. Nociception is a function of the nervous system and mediated by the transmission of electrical and chemical signals originating from peripheral nerve endings, passing through the spinal cord, and ultimately reaching the brain. Normal nociception is dependent upon many molecular events at multiple levels of the nervous system, from the peripheral nerve to the brain. Along the paths of nociception, the spinal cord is an important relay site where primary sensory inputs are integrated and propagated to the brain. In the spinal cord, noxious signals generated from peripheral sensory afferents traveling through synapses and are transmitted to secondary sensory neurons in superficial layers of spinal cord dorsal horn (SCDH). The SCDH neurons then transmit the noxious signal through ascending pathways to higher levels of the nervous system. Synapses between primary sensory inputs to the SCDH sensory neurons are affected by multiple pre- and post-synaptic inputs. This signal network involves signals from local spinal cord interneurons and other sensory neurons from deeper layers of the SCDH. In addition, there are descending pathways from the brain that serve as modulators for adjusting output signals of the SCDH projection neurons. Integration of these multiple mechanisms contributes to normal nociception.

In states of chronic inflammatory or neuropathic pain, this nociceptive function can become altered to induce abnormal sensory phenomena like allodynia and hyperalgesia. Allodynia is defined as increased nociception to normally innocuous stimuli (e.g., light touch), and hyperalgesia is defined as an excessive painful response to a painful stimulus (e.g., pin prick). This process involves plasticity by alteration of multiple neurotransmitters and

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intracellular signaling events in the spinal cord DH and is termed “central sensitization” [1]. Alteration in the production and secretion of neurotransmitters, neuropeptides, cytokines, and growth factors, changes in the expression or activity of the receptors for these secreted ligands, and frank changes in the physical interactions between cells (such as axonal sprouting) contribute to the development of central sensitization. This review will outline what is known about the molecular and cellular events involved in the process of central sensitization within the spinal cord, as well as the prospects for targeting these processes in the clinical treatment of chronic pain.

Normal nociception

Peripheral sensory inputs

In response to painful stimuli, action potentials are transmitted along sensory fibers to the cell bodies of corresponding primary sensory neurons in the dorsal root ganglia (DRG). The main peripheral nerve fibers for nociception are A δ and C fibers. These primary sensory afferent fibers carry painful signals from peripheral, mechanical, thermal and chemical stimuli. After converging afferent noxious signals from their peripheral processes, DRG neurons translate these electric pain signals and convert them into chemical signals by secreting neurotransmitters and neuropeptides into the SCDH. In general, peripheral afferent pain fibers can be divided into peptidergic and nonpeptidergic fibers, depending on their ability to express neuropeptides. Glutamate is the primary neurotransmitter expressed by nonpeptidergic fibers. Peptidergic fibers secrete both glutamate and neuropeptides, including substance P (SP) and calcitonin gene related peptide (CGRP). After painful stimuli, these neurotransmitters and neuropeptides are released from presynaptic terminals in the superficial layers (Rexed lamina I and II) of the SCDH, diffuse across the synaptic clefts, and bind to postsynaptic receptors on SC interneurons.

Spinal circuits for pain processing

In the SCDH, most primary nociceptive fibers synapse with secondary neurons and interneurons in lamina I and II. Most of these secondary nociceptive neurons and interneurons express NK1 receptor, the receptor for SP [2, 3]. NK1-positive neurons, which are found in the deeper layers of the DH, synapse with peptidergic sensory fibers in lamina I [2]. Conversely, NK1-negative sensory neurons that receive input signals from nonpeptidergic afferent fibers are located in lamina II of the DH. Dendrites from NK1-negative neurons interact with NK1-positive neurons in lamina I, which ultimately merge pain signals [4]. Furthermore, these neurons also interact with GABAergic and glycinergic interneurons in lamina II and III to serve as local modulators for inhibiting excessive nociceptive signals [5, 6].

Descending inhibitory pathways

In addition to local modulation by interneurons, there are descending inhibitory pathways from the brain that also communicate with SCDH neurons through chemical signals, including endogenous opioids, serotonin (5-HT), and norepinephrine (NE) [7]. The endogenous opioids are expressed from descending pathways originating from periaqueductal grey (PAG) matter. This pathway functions by activating opioid receptors on the pre- and post-synaptic endings in DH neurons.

Major noradrenergic inhibition originates at the locus coeruleus/subcoeruleus (LC/SC) and travels to the SCDH via the ventromedial funiculus. Evidence suggests that NE released from these inhibitory terminals acts via presynaptic α_2 receptors.

Most SC serotonergic inputs are from the nucleus raphe magnus in the caudal brainstem. These fibers descend to the SCDH to release 5-HT. At least twelve different 5-HT receptors mediate serotonergic actions in SCDH. They are either facilitatory or inhibitory in pain processing.

Glutamate receptors

Most painful signals in the DH are mediated by glutamate, the most abundant excitatory amino acid in the CNS. Glutamate actions are mediated by several glutamate receptors: the α -amino-3-hydroxy-5-methyl-4-izoxazolepropionic acid receptors (AMPA), the kainate receptors (KAR), and the *N*-methyl-D-aspartate receptors (NMDAR).

a. AMPA receptors—AMPA receptors are primary glutamate receptors that mediate nociception. AMPARs are ionotropic transmembrane molecules that mediate fast synaptic transmission in the central nervous system (CNS). AMPARs are composed of four types of subunits, designated as GluR1-4 [8, 9]. Most AMPARs consist of symmetric 'dimers of dimers' of GluR2 and either GluR1, GluR3 or GluR4 [10]. AMPARs are rapid channels, which means channels open and close quickly following ligand binding. This feature results in rapid depolarization of the cell membrane without a long repolarization phase and thus renders the neuron able to respond to high frequency stimulation. In fact, AMPARs mediate most of the fast excitatory synaptic transmissions in the CNS.

AMPA receptors that carry GluR2 subunits are sodium/potassium channels. The presence of GluR2 subunits inhibits Ca^{+2} permeability of AMPARs [11]. Since most AMPARs in the CNS have GluR2, AMPAR channel openings prevent inward calcium currents and protect neurons from calcium-mediated excitability [11].

b. Kainate receptors—Kainate receptors (KAR) are glutamate receptors with selective affinity for their agonist, kainate. They mediate excitatory postsynaptic neurotransmission by binding glutamate, but serve as presynaptic modulators to inhibit GABAergic neurons. Like AMPARs, KARs are located in both pre- and post-synaptic membranes and function as sodium/potassium channels [12]. Compared to AMPARs, their repolarization phase is longer, making them less responsive to high frequency stimulation [12].

c. NMDA receptors (NMDAR)—NMDARs are ionotropic glutamate receptors that selectively bind to NMDA. NMDARs are tetrameric ion channels consisting of two NR1 subunits in complex with two NR2 (A, B, C and D) or NR3 (A, and B) subunits [13]. In addition, alternative splicing of the GluN1 subunit yields eight possible variants of this subunit. The NR1 subunit contains a binding site for glycine or D-serine, whereas the NR2 subunit contains the glutamate binding site.

In the quiescent state, NMDARs are blocked by Mg^{2+} ions. Opening of other ionotropic receptors, such as AMPARs, causes membrane depolarization. During this process, the Mg^{2+} blockade is removed and allows a voltage-dependent flow of Na^{+} and Ca^{2+} ions into cells and K^{+} out of cells. The NMDAR-dependent calcium influx triggers a series of signaling cascades which involve activation of multiple protein kinases, including mitogen activated protein kinases (MAPK) and protein kinase C (PKC) [14]. This kinase activation further phosphorylates subunits of NMDARs and prolongs both channel opening and membrane depolarization. Because of this unique feature, NMDARs mediate many biological functions, including chronic pain, memory, and windup phenomenon (increased pain sensitivity after repeated stimuli) in distinct areas of the CNS [15].

d. Metabotropic glutamate receptor—Another glutamate receptor, metabotropic glutamate receptor (mGluR), also participates in pain processing. Unlike ionotropic glutamate receptors, mGluR are coupled with G protein-dependent actions to trigger intracellular secondary messengers. mGluR have 8 subtypes and many splice variant products. In general, mGluR1 and mGluR5 are better understood for pain processing compared to other isoforms. After noxious stimuli, these receptors respond to glutamate and activate phospholipase C/PKC pathways, which increase intracellular calcium levels [16].

Other neurotransmitters

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that is affected after noxious stimuli. GABA acts through GABA_A and GABA_B receptors. Upon GABA binding, the GABA_A receptors selectively open for Cl⁻ inflow and hyperpolarize the cell membrane of neurons. This causes an inhibitory effect on neurotransmission by blocking transmission of action potentials [17].

In contrast to ionotropic GABA_A receptor, GABA_B receptors are metabotropic transmembrane receptors. Through G-protein-coupled mechanisms, they open the K⁺ channels and prevent cell membrane depolarization and action potential transmission. In addition, GABA_B receptors can also reduce activity of adenylyl cyclase and decrease the cell's conductance to Ca²⁺.

Glycine is another major inhibitory neurotransmitter for modulating nociception. Actions of glycine are mediated by binding to glycine receptors (GlyR) that are distributed densely at superficial layers of the SCDH [18].

Neuropeptides

In painful states, afferent sensory fibers secrete increased levels of neuropeptides from their synapses with secondary neurons in the SCDH to mediate nociception. SP and CGRP are commonly associated with inflammatory and neuropathic models of pain. These neuropeptides are secreted from presynaptic terminals of A δ and C fibers and bind to their corresponding receptors (NK1 receptor for SP and CGRP receptors for CGRP) in both pre- and post-synaptic compartments in SCDH. Other neuropeptides involved in nociception include cholecystokinin, neuropeptide Y, and bradykinin.

Spinal cord mechanisms of chronic pain and clinical implications

There are several cellular and molecular mechanisms involved in the SC that are responsible for the development of chronic pain states:

1. Phenotype switch and neurotrophic factors

a. Pathology—After peripheral painful stimulation, A β fibers that normally do not process nociception become sensitive to noxious stimuli. These large-diametered myelinated sensory fibers conduct rapid nociceptive signals after inflammatory or neuropathic insults. In addition, they begin to express neuropeptides like SP and CGRP and neurotrophic factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) [19]. NGF is produced from peripheral tissues and retrogradely transported to DRG neurons. In DRG neurons, NGF binds to Trk A receptors and activates several protein kinases, including MAPK to upregulate expression of SP, CGRP, and BDNF that are then secreted into the DH by Trk A-positive afferent fibers. In the SCDH, most of BDNF's actions are mediated by the Trk B receptor. BDNF binding of Trk B receptors induces the receptors' intrinsic tyrosine kinase activity, which in turn activates a series of downstream signaling events [20]. As a result, peripheral sensory inputs to the SCDH are substantially increased and pain perception

is therefore exaggerated. Since SP, CGRP, and BDNF expression is dependent on NGF signaling, NGF is likely the key factor in this transformation of A β fibers.

b. Clinical implications—Currently, no treatment targets this mechanism in the development of chronic pain. Potential pharmacological approaches for inhibiting phenotype switch are: (1) Blocking neurotrophin signaling. Treatment approaches include anti-NGF and Trk A receptor blockade, which has been tested in clinical trials for treating chronic pain. A novel multipotent neurotrophin antagonist, 3-[(5E)-4-oxo-5-[[5-(4-sulfamoylphenyl)-2-furyl]methylene]-2-thioxo-thiazolidin-3-yl]propanoic acid (Y1036) has affinity for both NGF and BDNF and prevents their binding to Trk A and Trk B receptors [21]. In addition, inhibition of downstream signaling molecules, including MAPK, has proven to achieve analgesia in animal models [22]. (2) Inhibiting SP and CGRP actions. Several currently available treatments for chronic pain can inhibit SP and CGRP actions. Capsaicin, the spicy component of hot pepper, binds to the transient receptor potential vallinoid (TRPV)1 receptor and exhausts SP secretion to achieve analgesia [23]. Gabapentin and pregabalin are blockers of a voltage gated calcium channel, $\alpha 2\delta$. They decrease SC levels of neurotransmitters and neuropeptides, including SP and CGRP [24]. Several NK1 antagonists have been tested in clinical trials for chronic pain. However, these compounds have not been successful in demonstrating analgesia [25]. In contrast, a CGRP antagonist, Telcagepant (MK-0974), has shown efficacy against migraine [26].

2. Collateral sprouting

a. Pathology—In painful conditions, nerve endings from A β afferents in the lamina III-IV of the SCDH could sprout and synapse with secondary neurons in laminae I and II. This phenomenon is associated with chemical factors generated in the superficial lamina with increased nociception [27]. Potential causative factors are: (1) Tumor necrosis factor- α (TNF- α) and cytokines released from activated microglia and astrocytes. These factors are known to stimulate neurotrophic factor expression which in turn could promote collateral sprouting in DH [28]. (2) BDNF release from NGF-positive primary afferents. BDNF has multiple effects on Trk B-expressing neurons to potentiate spinal nociceptive transmission, including stimulation of axon outgrowth and collateral sprouting [29].

b. Clinical implications—Currently, no available medication blocks collateral sprouting. Based on the known mechanisms underlying collateral sprouting, inhibition of TNF- α , cytokines, and BDNF could be potential treatments to inhibit collateral sprouting after peripheral inflammation or nerve injury. In addition, NGF signaling blockade could also be a valuable approach since this treatment could result in dual action of pain control by decreasing the peripheral nociceptive inputs and eliminating the BDNF-mediated collateral sprouting in the SCDH.

3. Disinhibition

a. Pathology—GABAergic and glycinergic interneurons of SCDH normally serve as presynaptic regulators for excessive nociception. This mechanism could become defective after nerve injury. In animal models of chronic pain, the numbers of GABA and glutamate decarboxylase (GAD)-positive interneurons are decreased due to apoptosis [30]. This reduction of spinal inhibition results in hyperalgesia.

The actions of glycine receptors are also compromised during chronic pain. Prostaglandins released during chronic inflammatory conditions could deteriorate Glyc $\alpha 3$ function through EP2 receptors. This phenomenon is mediated by Gs protein and protein kinase A.

Other inhibitory systems involved in chronic pain include μ and δ -opioid receptors, α_2 -adrenergic receptor, purinergic A1 receptor, neuropeptide Y1 and Y2 receptors, cannabinoid CB1 and CB2 receptors, muscarinic M2 receptor, GABA_B receptor, and somatostatin [31].

b. Clinical implications—It is a common practice to use GABAergic drugs for treating chronic pain. Benzodiazepines, agonists for the GABA A receptor, and baclofen, a GABA B receptor agonist, have been proven to have analgesic actions. In addition, α_2 adrenoreceptor agonists (clonidine and tizanidine) could enhance GABAergic and glycinergic antinociception and have been applied for chronic painful conditions [32]. An increase of local GABA levels in the SCDH by using a herpes simplex viral vector-mediated gene transfer for glutamic acid decarboxylase (GAD) could also be a potential treatment to enhance GABAergic action in the SCDH [33]. Cyclooxygenase 1 and 2 inhibitors are potent medications for inhibiting PG production during inflammatory conditions. These medications could prevent inhibitory actions of PGs on Glyr α 3 and preserve the glycinergic inhibition in the SCDH.

NMDA receptor activation

c. Pathology: An essential step for augmented continuous pain is activation of NMDA receptors on SCDH neurons. After repetitive, prolonged, or intense stimulation, membrane depolarization on postsynaptic terminals of secondary sensory neurons from AMPA, NK1, CGRPR currents release the Mg²⁺ blockade of NMDA receptors, which opens the ion channel. This causes a significant amount of Ca²⁺ inward current and triggers a series of intracellular reactions by activation of several intracellular protein kinases. In consequence, enhanced channel conductance as well as receptor membrane trafficking contribute to prolonged membrane depolarization [1].

d. Clinical implications—Several NMDA receptor antagonists are available: Dextromethorphan was tested for treatment of pain. However, its efficacy is poor for analgesia and causes significant side effects [34]. Memantin is a medication for Alzheimer's disease that blocks NMDARs. Most trials failed to demonstrate an analgesic action [34]. Methadone is an opioid medication that has properties of NMDA blockade. Clinically, methadone is effective for treating multiple painful conditions. Its NMDA blockade is from *d*-methadone, one of the enantiomeric isoforms of methadone [35]. In addition, bupivacaine, a local anesthetic that blocks sodium channels, blocks the NMDA receptor, an action which is independent of its sodium channel blockade [36]. Ketamine, another anesthetic, is a potent NMDA receptor blocker, which, however, has significant side effects preventing long term use [37]. Amantadine, another NMDAR antagonist, has little value for treating chronic pain [38].

4. Other glutamate receptors

a. Pathology—In painful conditions, increased peripheral afferent inputs induce a conversion from GluR2-containing AMPAR (impermeable to Ca²⁺) to GluR1 (Ca²⁺ permeable) [39]. This subunit switch of AMPARs affects AMPA-dependent intracellular signaling. As a result, in addition to Na⁺ inflow after AMPA receptor activation, accompanied Ca²⁺ inward current triggers a wide variety of downstream intracellular activities, similar to NMDA receptor activation. This action further enhances response to painful stimuli in hyperalgesia. In addition to AMPAR, kainate receptors, and mGluR5 contribute to chronic pain [40, 41].

b. Clinical implications—There is no medication on the market specifically targeting AMPARs. NS1290, an AMPAR blocker, has been tested in a clinical trial and shows promising results in treating chronic pain [42]. Several antagonists are available for kainate

receptors. These compounds are potent against chronic pain in a variety of animal models [43]. Methylphenylethynylpyridine (MPEP) and its derivative, fenobam, are blockers for mGluR5 [41]. They both demonstrate good analgesic actions against chronic pain in animal studies. However, these compounds have not yet passed clinical trials.

5. Glial cell activation

a. Pathology—After peripheral inflammatory reaction or nerve injury, SC glial cells are activated and contribute to enhanced neuronal excitability. Microglia respond to these stimuli by releasing proinflammatory cytokines, including interleukin-1b and TNF- α . Microglia are activated by several chemical factors, including ATP and NO. After nerve injury, increased ATP levels trigger activation of microglial P2X4 receptors and induce cytokine expression via p38. In addition, other ATP receptors (ATPR), including P2X3, P2X7 and P2Y12, are also involved in microglia-mediated chronic pain [44].

In addition to microglia, increased numbers of activated astrocytes are detected in the corresponding the SCDH segment after painful stimuli. These cells are likely activated by local production of cytokines [45]. Both microglia and astrocytes express chemokines to promote pain sensitivity [46].

b. Clinical implications—Current effective treatments for inhibiting glial actions in chronic pain are still lacking. Minocyclin, a tetracycline antibiotic, has actions against microglia activation in the SC in painful conditions. In addition, propentofylline, a methylxanthine derivative, exhibits anti-hyperalgesia by limiting microglial actions and reducing SC levels of IL-1 β , IL-6, and TNF- α [47]. Several inhibitors for p38 have been tested in clinical trials for chronic pain [48]. Antagonizing ATP actions is an effective approach for inhibiting glial actions in chronic pain. Several antagonists for p2X3, p2X4, p2X7, and p2Y12 were reported to have promising analgesic efficacy in animal studies [44]. All these compounds have not yet proven to be effective for treating chronic pain in clinical trials. In addition, several inhibitors for interleukins, TNF- α and their corresponding receptors, are available for treating inflammatory conditions [49]. However, their roles for treating chronic pain are still unclear.

6. Activating descending pathways

Descending inhibitory pathways from endogenous opioid, NE and 5-HT systems in the brain control excessive nociception in normal conditions. Opioids are frequently used in treating chronic pain from either inflammatory or neuropathic origins. In addition, several other treatment modalities that trigger production of endogenous opioids have been widely used for treating chronic pain. These treatments are transcutaneous electric stimulation, acupuncture, vagal stimulation, spinal cord, and motor cortex stimulation [50]. For enhancing the NE inhibitory actions, α 2 agonists are frequently used for chronic pain to inhibit presynaptic action potentials as well as enhancing local GABAergic and glycinergic actions. Medications like tricyclic and tetracyclic antidepressants (TCAs) inhibit reuptakes of both 5-HT and NE and have been considered as the first line medication for neuropathic pain. Specific serotonin-norepinephrine reuptake inhibitors are more tolerable than TCAs and are frequently used for chronic pain by enhancing inhibitory actions from both systems.

Conclusion

Chronic pain is a complex condition that involves all levels of the nervous system. Along the neural axis, the SC is an important relay station where primary nociceptive inputs are modified through local and distant networks and transmitted to higher levels in the nervous system. The plasticity of SC neural circuits and their neurochemical properties build a strong

foundation for the development of chronic pain. Breaking these processes has been a challenge for pain researchers. Although current mechanism-specific treatments for SC-mediated pain are limited, basic science research provides evidence to suggest potential new directions for treating chronic pain. However, most of these new treatments have not yet passed placebo-controlled clinical trials. More effort is urgently needed to develop mechanism-specific treatments for chronic pain.

Acknowledgments

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Fig. 1.
Schematic description of the spinal cord mechanisms for chronic pain. See text for abbreviations and details.